REMARKS

In view of the following remarks, the Applicant respectfully requests allowance of Claims 1-4, 6-20 and 26-30, the only claims pending and under consideration in this application.

Formal Matters

Claims 1 and 26 have been amended to specify subjecting the array to the member of the plurality of different experimental conditions to produce gene expression data; evaluating the gene expression data by clustering the candidate probe sequences into one or more groups of candidate probe sequences based on each candidate probe sequence's collection of empirical gene expression data values to produce clustered probe sequences, in which each of the one or more groups exhibits substantially the same performance across the plurality of experimental conditions; and evaluating any remaining candidate probe sequences not among the clustered probe sequences. Support for this amendment can be found in the specification on page 22, lines 22-34 and page 34, line 14.

Claims 6 and 10 have been amended for clarity. Support for the amendments can be found in the original Claims 6 and 10.

Claims 17-25 have been canceled.

Claim 26 has been amended in a manner similar to Claim 1. Claim 26 has further been amended to specify reporting the identified candidate probe sequences to a user. Support for this amendment can be found in the specification on page 24, line 33 through page 25, line 29.

The remaining amendments to the claims are to make sure that, where appropriate, dependent claims terms have appropriate and clear antecedent basis, to correct typographical errors, and to correct errant dependencies.

Because these amendments add no new matter, entry thereof by the Examiner is respectfully requested.

Claims Under Examination

Nonelected Claims 17-25 have been canceled.

Claim Rejections – 35 USC § 101

Claims 26-30 were rejected under 35 U.S.C. 101 because these claims assertedly are drawn to non-statutory subject matter. While not agreeing with the position of the Office and solely in order to expedite allowance of the present application, the instant Claim 26 has been amended to recite reporting the identified candidate probe sequences to a user, as suggested by the Examiner. Accordingly, this rejection may be withdrawn.

Claim Rejections – 35 USC § 112

The Examiner rejects Claims 1-4, 6-16 and 26-30 under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement.

Specifically, the Office Action asserts that instant specification is not enabling for a method including steps of (i) identifying a plurality of candidate probe sequences based on selection criteria, (ii) empirically evaluating probe sequences under different experimental conditions, (iii) clustering probe sequences based on empirical data values, and (iv) and evaluating any remaining non-clustering probes for candidate probe sequences.

The Office Action states with regard to step (ii) that practice of the claimed method generally requires the evaluation of gene expression data, but that such limitations are not reflected in the instant claims.

Claims 1 and 26 now recite subjecting the array of candidate nucleic acid probes to a member of the plurality of different experimental conditions to produce gene expression data, and evaluating the gene expression data by clustering candidate probe sequences into one or more groups based on each candidate probe sequence's empirical data values.

As such, the instant claims (a) directly recite the evaluation of gene expression data, and (b) recite how such evaluation is to be conducted, with ample support for such evaluation in the specification (please consult pages 16-24). As such, the skilled artisan would readily understand from the claim language how to conduct an evaluation of gene expression so as to perform the claimed method.

Regarding step (iii), the Office Action further states that while the specification does provide a working example of clustering candidate probe sequences into one or more groups [p.32], it does not provide sufficient guidance as to how to cluster candidate probe sequences in groups where one or more groups exhibits substantially the same performance across experimental sets, failing to define the metes and bounds of "empirical values" and how one of ordinary skill in the art would identify or obtain the appropriate "empirical values" given the lack of description regarding the terms.

As discussed above, Claims 1 and 26 now recite subjecting the array of candidate nucleic acid probes to a member of the plurality of different experimental conditions to produce gene expression data, and evaluating the gene expression data by clustering candidate probe sequences into one or more groups based on each candidate probe sequence's empirical gene expression data values.

Present Claims 1 and 26 recite experimental conditions, which are described in the specification at page 16, for example. That section discloses that a plurality of differential gene expression experiments is used to obtain empirical gene expression data for each of the candidate nucleic acid probe sequences for each of the plurality of different conditions.

As such, the skilled artisan would readily understand from the claim language and the specification how to conduct an evaluation of gene expression so as to perform the claimed method.

Regarding step (iv), the Office Action further states that it remains unclear how candidate probe sequences that satisfy a signal intensity threshold are used to evaluate non-clustering probes since no correlation has been set forth in the instant claims relating non-clustering probes to signal intensity data.

The Applicants submit that instant Claims 1 and 26 now recite, *inter alia*, evaluating any remaining candidate probe sequences not among said clustered probe sequences for sequences that satisfy a signal intensity threshold.

As such, the relationship between candidate probe sequences which are not among the clustered probes and signal intensity threshold is clear, namely, that the signal intensity threshold of those remaining probe sequences is evaluated by methods known to the art and fully detailed in the specification (see page 23, line 4 through line 30).

Further, the law regarding enablement of inventions is clear: to comply with 35 U.S.C. § 112, first paragraph, a specification need only enable a skilled artisan to make and use the claimed invention without undue experimentation; "[t]he test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation."[1]

The Applicants submit that every technique leading up to and composing step (iv), namely, assigning candidate sequences to clusters thereby identifying candidate sequences which are not among those clusters (page 18, line 19 through page 23, line 2) and evaluating both the signal intensity (page 23, line 4 through line 30) and lack of signal variation (page 23, line 31 through page 24, line 32) in the candidate sequences

[1] *United States v. Telectronics, Inc.*, 8 USPQ 2d 1217, 1233 (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989). See also *Genentech, Inc. v. Novo Nordisk*, 42 USPQ 2d 1001 (Fed. Cir. 1997), *cert. denied*, 522 U.S. 963 (1997); *Scripps Clinic and Research Foundation v. Genentech, Inc.*, 18 USPQ 2d 1001 (Fed. Cir. 1991).

are fully and specifically detailed in the specification. The instant passages provide specific algorithms and techniques for using them to evaluate gene expression data as known in the art, lists specific signal intensity thresholds, specific log ratios for identifying low signal variation and provides incorporated references teaching how to determine those log ratios, in short, everything one of skill would require in order to readily perform the method steps as claimed.

Moreover, the instant specification provides a working example in which all of the claimed steps are performed to successfully identify 104 probes with signal intensities spanning the dynamic range of the microarray platform (pages 32-37 of the specification). Accordingly, a real working example is provided.

Further, the above guidance and working example is provided in an art acknowledged by the Office Action as having a high level of skill (Office Action, page 8) in the mature field of array technology.

The Office Action further states that since no steps directed to obtaining or identifying probes that are "non-clustering" are recited in the instant claims, it is unclear how the evaluation of "any" remaining non-clustering probes "for candidate sequences" results in the identification of candidate probes sequences that are suitable for use as a substrate surface immobilized normalization probe. The Office Action further asserts that it is unclear how the "non-clustering probes" are being evaluated.

The instant claims are directed to evaluating any remaining probes not among said clustered probe sequences for candidate probe sequences that satisfy a signal intensity threshold and exhibit substantially no variation in signal. As such, the relationship between the identification of clustered probes and probes which remain (i.e., one of simple exclusion) is clear from the plain language of the claims.

Further, as established above, the instant specification more than adequately details how the evaluation of the remaining probes is to proceed. The Applicants believe this aspect of the rejection to have been adequately addressed.

The Office Action cites Ben-dor et al. ("Ben-dor") and Alon et al. ("Alon") which discuss statistical methods of gene clustering. The Office Action additionally cites Kane et al. ("Kane"), asserting that "most clustering analysis experiments consist of some comparative steps (e.g., mutants compared to a reference) and evaluation of data using some statistical correlation methods as well" (Office Action, page 7).

Note, however, that Kane does not teach, or even discuss, clustering of any kind. The cited Figure 1 of Kane shows a comparison chart which simply averages and reports the data as measured within the bounds of precision for three genes, *thr*, *dap* and *trp*; as such Kane does not show algorithmic treatment to produce clustering analyses such as those performed by Ben-dor and Alon (see Ben-dor, Fig 3, where n=256 simulated genes; Color Plate 1, where n=112 genes; Figure 6, where n=1246 genes; Figure 7, where n=2000 genes; Alon, throughout the reference, where n=2000 genes).

Further, both Ben-dor and Alon teach that the clustering itself does not involve any comparative steps (Ben-dor, pages 282-283; Alon, page 6746, right column, entitled "Data Clustering."

Indeed, Ben-dor processes the data of Alon, which contains tumor and normal tissue, specifically to demonstrate that the CAST algorithm used by Ben-dor, and cited by the present specification, reliably places the tumor tissue in one of the clusters *without* prior reference to the identity of the tissue (Ben-dor, page 294). With regard to such tissue clustering, Ben-dor states that it is "another interesting application of clustering in gene expression." As such, Ben-dor teaches that gene clustering need not involve any "comparative steps" as stated in the Office Action.

Practitioners in the chemical and molecular biology arts frequently engage in extensive modification of reaction conditions and complex and lengthy experimentation where many factors must be varied to succeed in performing an experiment or in producing a desired result. The Federal Circuit has found that such extensive experimentation is not undue in the molecular biology arts. For example, the court concluded that extensive screening experiments, while being voluminous, were not undue in view of the art which routinely performs such long experiments.[2]

Ben-dor teaches that based on its model, "the algorithm reconstructs the clustering with high probability" (page 282). As such, the clustering method taught by Ben-dor, and referenced by the present specification, has a high probability of success. It is well known that the array arts are well disposed to the performance of large experiments without undue effort.

Moreover, the present claims are directed to a method of identifying a sequence of a nucleic acid that is suitable for use as a substrate surface immobilized normalization probe. The method does not classify tissue. As such, the Applicants submit that the objections raised on this point by the Office Action are not relevant to the rejected claims.

The Applicants submit that this aspect of the rejection has been adequately addressed.

In view of the foregoing discussion, and given the amount and type of guidance provided in the specification, the high level of skill in the art, and the predictability of the well-known methods invoked by the present application, the Applicants submit that the ordinarily skilled artisan can readily perform each step in the method as claimed.

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[2] *Hybritech v. Monoclonal Antibodies, Inc.* 231 USPQ 81 (Fed. Cir. 1986)

Accordingly, Applicant's specification describes the claimed invention in such a manner that the invention may be practiced without undue experimentation. As such, Claims 1-4, 6-16 and 26-30 are fully enabled by the specification under 35 U.S.C. §112, first paragraph and withdrawal of this rejection is respectfully requested.

Claim Rejections – 35 USC § 112

The Examiner rejects Claims 1-4, 6-16 and 26-30 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Specifically, the Examiner states that since there is no previous recitation of non-clustering probes or any step directed to obtaining "non-clustering probes", there is lack of antecedent basis for this limitation, and that it is further unclear whether the non-clustering probes are being directly evaluated based on signal intensity threshold, signal variation, or some other method.

Instant Claims 1 and 26 now recite evaluating any remaining candidate probe sequences not among said clustered probe sequences for sequences that satisfy a signal intensity threshold.

As such, the Applicants submit that the concerns raised by the Office have been addressed regarding this aspect of the rejection.

The Office Action further states that it is unclear in what way the steps of claim 3 further limit claim 2.

Claim 2 recites "at least one selection criteria;" i.e., any or all of the three criteria (i), (ii) and (iii) may be chosen for inclusion in step (a) according to Claim 2.

Claim 3 further limits Claim 2 by specifying that all three criteria must be employed. Therefore, the number of options presented by Claim 2 is reduced to a single option by Claim 3.

As such, Claim 3 further limits Claim 2, and this aspect of the rejection may be withdrawn.

The Examiner has stated that Claim 3 should be corrected to recite "are employed in said identifying step."

The Applicants have amended Claim 3 according to the Examiner's recommendation. As such, this aspect of the rejection may be withdrawn.

The Office Action states that the limitation of Claim 6 reciting "each member ... is a different tissue/cell line differential gene expression assay" is unclear because of the use of the mark "/".

The Applicants have amended Claim 6 to recite wherein each member of the plurality of different experimental conditions is a different differential gene expression assay performed on a tissue or cell line. As such, this aspect of the rejection may be withdrawn.

The Office Action states with regard to Claim 10 that it is unclear whether "considered to exhibit" is intended to be an active method step or a further limitation of said probe sequence.

The Applicants have amended Claim 10 to recite in which a candidate probe sequence exhibits substantially no variation in signal under said plurality of different experimental conditions if its log ratio is not significantly different than zero across the

plurality of different experimental conditions. As such, this aspect of the rejection may be withdrawn.

The Office Action states that "non-clustering probes" in Claim 26 lacks antecedent basis.

Instant Claims 1 and 26 now recite evaluating any remaining candidate probe sequences not among said clustered probe sequences for sequences that satisfy a signal intensity threshold.

In view of the foregoing discussion, the Applicants submit that Claims 1-4, 6-16 and 26-30 satisfy the requirements of 35 U.S.C. §112, second paragraph.

CONCLUSION

The Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone John Brady at (408) 553-3584.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-1078, order number 10030468-1.

Respectfully submitted,

Date: March 23, 2007

By: _____
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